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Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/826,519	Applicant(s) INNIS ET AL.	
	Examiner Lauren Nguyen	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 is/are rejected.

7)☒ Claim(s) 8 is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

KATRINA TURNER
PATENT ANALYST

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Applicants sequence listing from parental application, 09/648,254, was used to search sequences for this instant application.

2. During a telephone conversation with David Lentini on 19 July 2001, Applicant confirmed that claim 7 recites a typographical error of "...3-to-3' linked nucleotide." Applicant stated that the correct recitation of claim 7 should be "...3'-to-3' linked nucleotide." Therefore, the Examiner conducted the prior art search for claim 7 to recite a "...3'-to-3' linked nucleotide."

Election/Restrictions

3. Restriction to one antisense oligonucleotide or to a set of antisense oligonucleotides directed to one target, as recited within claim 8, is required under 35 U.S.C. 121.

I. SEQ ID No. 1, drawn to antisense oligonucleotide sequence targeted to AKT1 gene, classified in class 536, subclass 24.5, for example.

II. SEQ ID No. 2, drawn to antisense oligonucleotide sequence targeted to AKT2 gene, classified in class 536, subclass 24.5, for example.

III. SEQ ID No. 3, drawn to antisense oligonucleotide sequence targeted to CHK1 gene, classified in class 536, subclass 24.5, for example.

IV. SEQ ID Nos. 4 and 5, drawn to antisense oligonucleotide sequence targeted to CHK2 gene, classified in class 536, subclass 24.5, for example.

V. SEQ ID No. 6, drawn to antisense oligonucleotide sequence targeted to CK1E gene, classified in class 536, subclass 24.5, for example.

VI. SEQ ID Nos. 7 and 8, drawn to antisense oligonucleotide sequence targeted to E1AF gene, classified in class 536, subclass 24.5, for example.

VII. SEQ ID Nos. 9 and 10, drawn to antisense oligonucleotide sequence targeted to IGFR1 gene, classified in class 536, subclass 24.5, for example.

VIII. SEQ ID No. 11, drawn to antisense oligonucleotide sequence targeted to ILK gene, classified in class 536, subclass 24.5, for example.

IX. SEQ ID Nos. 12 and 13, drawn to antisense oligonucleotide sequence targeted to KRAS gene, classified in class 536, subclass 24.5, for example.

X. SEQ ID Nos. 14 and 15, drawn to antisense oligonucleotide sequence targeted to MMP2 gene, classified in class 536, subclass 24.5, for example.

XI. SEQ ID No. 16, drawn to antisense oligonucleotide sequence targeted to MMP9 gene, classified in class 536, subclass 24.5, for example.

XII. SEQ ID Nos. 17 and 18, drawn to antisense oligonucleotide sequence targeted to mTyr gene, classified in class 536, subclass 24.5, for example.

XIII. SEQ ID Nos. 19 and 20, drawn to antisense oligonucleotide sequence targeted to p110-alpha gene, classified in class 536, subclass 24.5, for example.

XIV. SEQ ID Nos. 21 and 22, drawn to antisense oligonucleotide sequence targeted to p110-beta gene, classified in class 536, subclass 24.5, for example.

XV. SEQ ID No. 23, drawn to antisense oligonucleotide sequence targeted to PDK1 gene, classified in class 536, subclass 24.5, for example.

XVI. SEQ ID No. 24, drawn to antisense oligonucleotide sequence targeted to UPAR gene, classified in class 536, subclass 24.5, for example.

These inventions are distinct, each from the other because of the following reasons:

Inventions I-XVI are distinct chemical entities with different chemical and biological properties, as evidenced by unique oligonucleotide sequences listed in Table 1 of the specifications. Moreover, the antisense oligonucleotide(s) of each Group are distinct, each from the other, because they are targeted to different genes which have unique biological functions and are differentially expressed, for instance. Therefore, for the reasons given above, restriction for examination purposes as indicated is proper.

During a telephone conversation with David Lentini on 10 July, 2001, a provisional election was made without traverse to prosecute and search SEQ ID Nos. 9 & 10, drawn to antisense oligonucleotides targeted to the IGFR1 gene, as recited within claim 8. Affirmation of this election must be made by applicant in replying to this Office action. SEQ ID Nos. 1-8 and 11-24, as recited within claim 8, are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-8 are examined only in so far as they read on the provisionally elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamond *et al.* (FEBS, Vol. 325 p. 123-127, 1993), Kandimalla *et al.* (Nucleosides and Nucleotides, Vol. 14, p. 1031, 1995), Ma *et al.* (Biotechnology Annual Review, Volume 5, p. 155-195), and Baracchini *et al.* (U.S. Patent No. 5,801,154).

The instant invention is drawn to a chimeric oligonucleotide having the structure: 5'-W-X^1-Y-X^2-Z-3' wherein W represents a 5'-*O*-alkyl nucleotide and the alkyl groups are lower alkyl groups (claim 2); each of X^1 and X^2 represents a block of seven to twelve phosphodiester-linked 2'-*O*-alkyl ribonucleotides and the alkyl groups are lower alkyl groups and is methyl (claim 2, claim 3); Y represents a block of five to twelve phophorothioate-linked deoxyribonucleotides; and Z represents a blocking group effective to block nuclease activity at the 3'end of the

oligonucleotide (claim 1). The 5'-*O*-alkyl nucleotide claimed is 5'-*O*-alkyl thymidine (claim 4) and is linked to X^1 via a phosphodiester or phosphorothioate linkage (claim 5). Claimed group Z of said chimeric oligonucleotide is linked to X^2 via a phosphotriester, phosphorothioate, or a phosphoradmidate linkage (claim 6).

Lamond *et al.* have taught the use of 2'-*O*-alkyl ribonucleotides in antisense oligonucleotides and the advantage of this modification in imparting resistance to "a wide range of RNA and DNA specific nucleases (p.123)." Lamond *et al.* teaches the use of 2'-*O*-alkyl ribonucleotides as antisense probes (page 125, for example). Lamond *et al.* also teaches that the 2'-*O*-alkyl group is a lower alkyl group and is explicitly a 2'-*O*-methyl ribonucleotide (p.123, paragraph 3). Lamond *et al.* does not teach chimeric oligonucleotides with phosphorothioate linkages, 5'-*O*-alkyl nucleotide, or a 3' blocking group.

Kandimalla *et al.* have taught the synthesis of chimeric oligonucleotides containing 2'-*O*-alkyl ribonucleotides, in this instance the alkyl ribonucleotides are 2'-*O*-methylribonucleotide, and deoxyribonucleotides with a modified phosphate linkage. Kandimalla *et al.* does not teach phosphorothioate linkages expressly, 5'-*O*-alkyl nucleotide, or a 3' blocking group. Kandimalla *et al.* do not specifically teach chimeric oligonucleotides wherein the block of phosphodiester-linked 2'-*O*-alkyl ribonucleotides or the block of phophorothioate-linked deoxyribonucleotides is specifically seven to twelve nucleotides in length.

Baracchini *et al.* have taught substitutions on the sugar moieties of antisense oligonucleotides at the 5' position of the 5' terminal nucleotide (column 7, line 12-). Said substitutions comprise of lower alkyl, alkoxyalkoxy, and substituted lower alkyl groups (column 6, line 59-). Baracchini *et al.* do not specifically teach chimeric oligonucleotides wherein the

block of phosphodiester-linked 2'-*O*-alkyl ribonucleotides or the block of phophorothioate-linked deoxyribonucleotides is specifically seven to twelve nucleotides in length.

Ma *et al.* have taught the modified phophorothioate linkage and the advantages said modification imparts on cellular uptake and nuclease protection of synthetic oligo-deoxyribonucleotides (page 156). In addition, Ma *et al.* have taught the addition of a 3' group on synthetic oligonucleotides, in this instance an acridine linkage, to prevent destruction by exonucleases (page 168). Ma *et al.* does not teach 5'-*O*-alkyl nucleotides in oligonucleotides.

One of ordinary skill in the art would have been motivated to make a chimeric oligonucleotide having the structure 5'-W-X^1-Y-X^2-Z-3', wherein W, X^1, Y, X^2, and Z have been defined above since Kandimalla *et al.* have taught to make chimeric oligonucleotides containing 2'-*O*-alkyl ribonucleotides and Ma *et al.* have taught using phophorothioate linkages in oligonucleotides to increase cellular uptake and nuclease protection of said oligonucleotides. In addition, one of ordinary skill would have been motivated to make and use a blocking group to reduce nuclease activity at the 3' end of the oligonucleotide since Ma *et al.* have taught that the addition of a 3' acridine group on synthetic oligonucleotides prevents destruction by exonucleases. Furthermore, the ordinary skilled artisan would have been motivated to make said chimeric oligonucleotides comprising of 2'-*O*-alkyl ribonucleotides, wherein said alkyl group is a lower alkyl groups and is expressly a methyl group, because Lamond *et al.* have taught the advantage of increased resistance to RNA and DNA specific nucleases when oligonucleotides are incorporated with 2'-*O*-methyl ribonucleotides. One of ordinary skill in the art would also have been motivated to make said chimeric oligonucleotide comprising of a 5'-*O*-alkyl nucleotide, wherein said alkyl group is a lower alkyl group and said nucleotide is a thymidine,

since Baracchini *et al.* have taught lower alkyl substitutions at the 5' position of the 5' terminal nucleotide in oligonucleotides wherein said nucleotide can be thymidine. Since the ribonucleotide range of seven to twelve in X^1 and X^2 and the deoxyribonucleotide range of five to twelve in Y does not appear to impart any benefit or advantage other than the properties taught in the prior art, one of ordinary skill would have been motivated to make and use any range of nucleotides in the chimeric oligonucleotide by design choice without evidence to the contrary.

One of ordinary skill would have had a reasonable expectation of success in making said chimeric oligonucleotide having the structure 5'-W-X^1-Y-X^2-Z-3', wherein W, X^1, Y, X^2, and Z have been defined above since Kandimalla *et al.* have taught making chimeric oligonucleotides containing 2'-*O*-alkyl ribonucleotides and Ma *et al.* have taught using phophorothioate linkages in oligonucleotides. In addition, one of ordinary skill would have had a reasonable expectation of success in making and using a blocking group to reduce nuclease activity at the 3' end of the oligonucleotide since Ma *et al.* have taught that the addition of a 3' acridine group on synthetic oligonucleotides prevents destruction by exonucleases. Furthermore, the ordinary skilled artisan would have had a reasonable expectation of success in making said chimeric oligonucleotides comprising of 2'-*O*-alkyl ribonucleotides and a 5'-*O*-alkyl nucleotide, wherein said alkyl group are lower alkyl groups and is expressly a methyl group for the 2'-*O*-alkyl ribonucleotides, because Kandimalla *et al.* have taught the synthesis of chimeric oligonucleotides containing 2'-*O*-methylribonucleotide and Baracchini *et al.* have taught chimeric oligonucleotides comprising of a 5'-*O*-alkyl nucleotide, wherein said alkyl group is a lower alkyl group.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

5. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lamond *et al.* (FEBS, Vol. 325 p. 123-127, 1993), Kandimalla *et al.* (Nucleosides and Nucleotides, Vol. 14, p. 1031, 1995), Ma *et al.* (Biotechnology Annual Review, Volume 5, p. 155-195), and Baracchini *et al.* (U.S. Patent No. 5,801,154) as applied to claims 1-6 above, in view of Rosch *et al.* (U.S. Patent No. 5,750,669).

The instant invention is drawn to a chimeric oligonucleotide having the structure 5'-W-X^1-Y-X^2-Z-3' wherein W represents a 5'-*O*-alkyl nucleotide; each of X^1 and X^2 represents a block of seven to twelve phosphodiester-linked 2'-*O*-alkyl ribonucleotides; Y represents a block of five to twelve phophorothioate-linked deoxyribonucleotides; and Z represents a blocking group effective to block nuclease activity at the 3'end of the oligonucleotide wherein Z is a 3'-to-3' linked nucleotide.

Rosch *et al.* have taught the preparation and introduction of a 3'-3' thymidyl-thymidine linkage into oligonucleotides to increase stability towards nuclease degradation (see Abstract and Example 2).

One of ordinary skill in the art would have been motivated to make a chimeric oligonucleotide having the structure 5'-W-X^1-Y-X^2-Z-3', wherein groups W, X^1, Y, X^2, and Z are defined above based upon the combined teachings of Lamond *et al.*, Kandimalla *et al.*, Ma *et al.*, and Baracchini *et al.* because of the reasons cited above in item #4 of this Office Action. Moreover, one of ordinary skill in the art would have been motivated to make said chimeric oligonucleotide comprising a blocking group effective to block nuclease activity at the 3'end of the said oligonucleotide wherein said blocking group is a 3'-to-3' linked nucleotide since Rosch

et al. have taught that the introduction of a 3'-3' thymidyl-thymidine linkage into oligonucleotides increases stability towards nuclease degradation.

One of ordinary skill would have had a reasonable expectation of success in making said chimeric oligonucleotide having the structure 5'-W-X^1-Y-X^2-Z-3', wherein W, X^1, Y, X^2, and Z have been defined above, based upon the combined teachings of Lamond *et al.*, Kandimalla *et al.*, Ma *et al.*, and Baracchini *et al.* for the reasons cited above in item #4 of this Office Action. Moreover, one of ordinary skill in the art would have had a reasonable expectation of success in making and using said chimeric oligonucleotide comprising a blocking group effective to block nuclease activity at the 3'end of the said oligonucleotide wherein said blocking group is a 3'-to-3' linked nucleotide because Rosch *et al.* have taught that the preparation and introduction of a 3'-3' thymidyl-thymidine linkage into oligonucleotides, as discussed in Example 2, for instance.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> *The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.*

6. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claim 7 fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the specification and is based upon the telephone conversation with David Lentini discussed above

in item #2 of this Office Action. In that telephone conversation, applicant has stated that the correct recitation of claim 7 should be "...3'-to-3' linked nucleotide" and Applicant indicated that the invention is different from what is recited in the claim because the claim recites a typographical error of "...3-to-3' linked nucleotide."

7. Claims 6 and 8 are rejected under 35 U.S.C. 112, second paragraph, as lacking proper antecedent basis. Claims 6 and 8 recite the limitation of "...group Z..." and "segment X^1-Y-X^2," respectively. There is insufficient antecedent basis for this limitation in said claims.

Objection

8. Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims and amended to read on the elected subject matter.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lauren Nguyen, Ph.D. whose telephone number is 703-308-0256. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lauren Nguyen, Ph.D.
July 24, 2001

SEAN McGARRY
PRIMARY EXAMINER